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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/609,133	SARFARAZI ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2006 and 22 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *5-7 and 11-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Result 9 from sequence search: AAH57391.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-4 and 8-10, species: SEQ ID NO: 1, in the reply filed on 4/27/2006, and the election (restriction requirement) of an alteration of GAG to AAG at codon 50 for claims 3 and 10, in the reply filed 5/22/2006 is acknowledged. The traversal is on the ground(s) that restriction between the sequences of SEQ ID NOS 1, 3, and 5 is improper as the sequences are not distinct and independent inventions. The response cites paragraph 16 of the specification and states that SEQ ID NOS 1, 3, and 5 are different isoforms of optineurin. The response argues that restriction to SEQ ID NOS 1, 3, and 5 should have been made as an election of species. This argument has been found persuasive as the different isoforms encode the same protein. Accordingly, the restriction requirement between SEQ ID NOS 1, 3, and 5 is considered a species election as follows:

This application contains claims directed to the following patentably distinct species: SEQ ID NOS 1, 3, and 5. The species are independent or distinct because they are drawn to structurally distinct nucleic acid molecules.

Applicant has elected SEQ ID NO: 1 for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, no claim is generic.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election,

applicant must indicate which are readable upon the elected species. MPEP § 809.02(a). The species requirement is made FINAL.

2. Further traversal in the response dated 5/22/2006 is on the grounds that all the mutations in claims 3 and 10 are mutations in the optineurin gene and that searching each of the mutations would not present a serious burden. This argument has been thoroughly reviewed but was not found persuasive as each mutation is structurally distinct and results in a structurally distinct protein. Searching each mutation presents a search burden. Search for a mutation at codon 50 would not necessarily provide information for a mutation at codon 322. Accordingly, a separate search must be conducted in the patent databases, the non patent literature, as well as sequence databases for each mutation.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. The instant invention claims priority to a number of applications as follows: the instant application is a CIP of 10/281,457, which is a continuation of 10/090,118, which is a CIP of 10/060,981, which claims benefit to 60/344,754.

Claims 1-4 have been awarded priority benefit of the filing date of 2/28/2002, the filing date of application 10/090,118. None of the claims have been awarded benefit of priority to the '981 or the '754 applications as the applications do not teach the sequence of SEQ ID NO: 1. Although both applications refer to Genbank Accession number AF420371, the sequence was not publicly available until Feb. 11, 2002. None of the additional cited sequences in Genbank Accession numbers or references appear to be the exact sequence of SEQ ID NO:1. Therefore,

the disclosure in the '981 and '754 applications do not meet the provisions of 35 USC 112/first paragraph.

Claims 8-10 have not been awarded benefit of any of the priority applications as none of the applications appear to provide support for an array of nucleic acid molecules. Accordingly, the filing date of claims 8-10 is 2/26/2003.

Specification

4. The amendment filed 5/24/2004 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows:

The amendment at page 6, paragraph 14 to "occurring in patients with sporadic glaucoma" is not supported by the specification. The specification does not teach what "sporadic glaucoma" is. The amendment replaces the recitation of "sporadic mutations", which does not support "sporadic glaucoma". One refers to cases of mutations, while the other refers cases of disease. The response asserts that support can be found at page 53 of the specification. The specification has been thoroughly reviewed. At page 53, the specification recites "familial and 15 of 124 sporadic individuals". The specification does not refer to "sporadic glaucoma" nor does it provide any definition for "sporadic glaucoma.

The amendment to insert the paragraph after paragraph 14 has 8 sentences. The specification was found to provide support for sentences 1 and 2 (at page 6, paragraph 15), as well as 7 and 8 (at page 36, paragraph 92). However, paragraph 15 of the specification discusses

detection, screening, prognosis, and diagnosis as being achieved by detecting the presence or absence of an alteration in the optineurin gene. This disclosure does not provide support for the definitions added in lines 3-6. The definitions provided at lines 3-6 further define species of "diagnosis" as well as species of "prognosis" which are not supported by the specification as filed. The use of dictionary definitions represents further definition of the terms in the specification after the filing date and is therefore considered new matter. The responses' citation of the specification at page 61, para 148 is not found persuasive as the specification does not provide support for the specific definition of diagnosis to include "analyzing the signs and symptoms of disease" (sentence 3). Further the specification at paragraph 16 and 129 do not provide support for diagnosis as including "analysis of the family history of the patient and determination of clinical symptoms of glaucoma". None of the cited specification paragraphs provide for the additional limitations set forth in the definition of "prognosis" in sentences 5-6.

The specification at page 10, paragraph 24, supports the amendment made in the same paragraph.

The amendment at page 28, paragraph 75 is not supported by the specification at page 33, paragraph 85 because the recitation of an antibody in paragraph 85 does not provide support for generally any "optineurin therapeutic agent". Additionally, it is not apparent that the omission of "mutant" in the amended paragraph was an obvious error given that the therapeutic agent in paragraph 75 is defined as enhancing or inhibiting polypeptide activity. Accordingly, the addition of the term "mutant' in paragraph 75 provides for a specific embodiment which was not supported by the specification as originally filed.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 4, and 8-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to nucleic acid molecules that comprise: a) SEQ ID NO: 1, b) an oligonucleotide of about 10 to about 50 nucleotides of SEQ ID NO: 1, or c) a complement of a or b, wherein the nucleic acid molecule has an alteration in at least one nucleotide, wherein the alteration is indicative of the presence of an optineurin associated glaucoma or an optineurin associated risk of glaucoma. The claims are further drawn to alterations that produce a sequence change in the protein, arrays comprising such nucleic acids, as well as further limiting "glaucoma" to POAG.

Claims 1 and 8 specifically recite that the nucleic acid molecule comprises an oligonucleotide of 10 to 50 nucleotides. The term comprising, however encompass any molecule that contains the indicated oligonucleotide, which encompasses genomic sequences which include introns, promoters, enhancers, etc. The specification, however, only teaches the cDNA of 3 different optineurin isoforms. The specification does not teach any genomic sequences of

optineurin. The claims, therefore, not only encompass alterations in SEQ ID NO: 1, but also include alterations in genomic sequences which have not been taught or described by the specification. The cDNA isoforms taught in the specification are not representative, structurally or functionally, of the number of possible variants, homologs, or unrelated sequences which could be associated with glaucoma. The claims encompass sequences that have not been taught or described by the specification, including sequences not known in the art at the time the invention was filed. For example, Accession number CAI16552, available after the filing date of the instant invention, teaches a protein sequence which differs from that predicted to be encoded by instant SEQ ID NO: 1.

Further, claims 1-2, 4, and 8-9 encompass a large genus of nucleic acids which comprise polymorphisms in any optineurin (OPTN) gene or coding sequence, which are not disclosed in the specification. The genus includes an enormous number of polymorphisms and mutations for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named 4 mutations (Table 1) for which data is provided. This data, however, does not provide for a predictable association with any type of optineurin associated glaucoma, which is broadly defined by the specification to include both juvenile and adult onset POAG, NTG/NPG, the low tension subgroup of POAG, as well as any glaucoma in which optineurin is implicated. Further, only the 2 mutations: E50K and M98K were found to have a statistically significant p value. Thus, applicant has express possession of only 2 particular disease associated mutations in SEQ ID NO: 1, in a genus which comprises hundreds of millions of different possibilities. Additionally, the specification teaches a number of additional mutations and polymorphisms in tables 2 and 3 (pages 56 and 57) which do not appear

to be associated with glaucoma. The mutations in table 2 are identified merely as "sequence alterations", however the specification does not teach if they are associated in any way with glaucoma. The specification teaches that the alterations in table 3 "may be either DNA polymorphisms or may be associated with the presence of glaucoma". However, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms vs disease associated alterations. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating an alteration or polymorphism with glaucoma is provided. Further, these claims encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at thousands of different sites. However, no predictable correlation between the structural alterations of the 2 mutations disclosed and a risk or association to glaucoma is provided by the specification. The specification does not teach the function of optineurin, nor how alterations are associated with glaucoma or an increased risk for glaucoma so that the skilled artisan would be able to distinguish between alterations indicative of "optineurin associated glaucoma" or "optineurin associated risk of glaucoma" from non glaucoma associated alterations.

The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms with glaucoma. The mutations shown are not representative of the genus of any alteration associated with an "optineurin associated" glaucoma because it is not clear which alterations within the OTPN gene would have the same affect. The specification does not teach whether the polymorphisms shown affect the function of optineurin. The

specification does not teach the function of optineurin nor how it's function, or lack of function, or altered function are predictably associated with glaucoma.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. As such, one of skill in the art would not recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the

invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

7. Claims 1-4, and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The specification, while being enabling for a) an isolated nucleic acid molecule comprising SEQ ID NO: 1 where position 458 is an A, and b) a nucleic acid molecule consisting of 10-50 contiguous nucleotide of SEQ ID NO: 1, wherein the nucleic acid molecule includes nucleotide position 458 of SEQ ID NO: 1 and wherein the nucleotide at position 458 is an A, c) the complement of either a or b, as well as an array of nucleic acid molecules attached to a solid support, the array comprising a nucleic acid molecule consisting of 10-50 contiguous nucleotide of SEQ ID NO: 1, wherein the nucleic acid molecule

includes nucleotide position 458 of SEQ ID NO: 1 and wherein the nucleotide at position 458 is an A, or the complement thereof, does not provide enablement for an isolated nucleic acid molecule or an array comprising a nucleic acid molecule as set forth in the claims. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claims are drawn to nucleic acid molecules that comprise: a) SEQ ID NO: 1, b) an oligonucleotide of about 10 to about 50 nucleotides of SEQ ID NO: 1, or c) a complement of a or b, wherein the nucleic acid molecule has an alteration in at least one nucleotide, wherein the alteration is indicative of the presence of an optineurin associated glaucoma or an optineurin associated risk of glaucoma. The claims are further drawn to alterations that produce a sequence change in the protein, as well as an alteration at codon 50 from GAG to AAG, arrays comprising such nucleic acids, as well as further limiting "glaucoma" to POAG.

The nature of the claimed invention, therefore requires the knowledge of predictable associations between the presence of any mutation in any OPTN gene, coding sequence, variant or homolog and association to any type of glaucoma.

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches screening a group of 54 adult onset glaucoma families for mutations in exon 4 of optineurin and detection of a missense mutation at codon 50 of GAG to AAG (position 458 of SEQ ID NO: 1) encoding a lysine instead of Glutamate (page 53). This specification teaches a statistically significant association for this mutation in affected families vs controls (as well as a statistically significant association for the M98K alteration as "risk associated" (page 53). The p values for the AG insertion and R545Q alteration, however, do not appear statistically significant (p=.187 and .315 respectively). Furthermore, the specification teaches a number of additional mutations and polymorphisms in tables 2 and 3 (pages 56 and 57) which do not appear to be associated with glaucoma. The mutations in table 2 are identified merely as "sequence alterations", however the specification does not teach if they are associated in any way with glaucoma. The specification teaches that the alterations in table 3 "may be either DNA polymorphisms or may be associated with the presence of glaucoma".

This data, however, does not provide for a predictable association with any type of optineurin associated glaucoma , which is broadly defined by the specification to include both juvenile and adult onset POAG, NTG/NPG, the low tension subgroup of POAG, as well as any glaucoma in which optineurin is implicated. The specification does not teach analysis with patients with juvenile onset open angle glaucoma.

Further, the specification does not teach the function of the OPTN gene, or how the mutations detected affect the function of the OPTN gene, such that one of skill in the art could establish that a predictable correlation exists between the presence of any mutation in OPTN and glaucoma or be able to predictably determine which alterations are indicative of "optineurin associated glaucoma" or "optineurin associated risk of glaucoma" vs non glaucoma associated alterations.

In light of the unpredictability taught in the art with regard to these factors, the specification does not enable one of skill in art to practice the method as broadly as it is claimed, without undue experimentation.

The state of the prior art and the predictability or unpredictability of the art:

At the time the invention was filed, the function of optineurin was not known, and the art provided no predictable structure function correlation between any mutations in the coding region of OPTN and risk of onset of glaucoma. Rezaie (Rezaie et al; Science, vol. 295, pages 1077-1079, 2/2002) teaches that the function of OPTN is unknown and that it has no significant homology to any protein (page 1079, end of col. 1). While Vittitow (Vittitow et al; Biochemical and Biophysical Research Communications, vol. 298, pages 67-74, 2002) teaches that expression of optineurin is increased in response to increased intraocular pressure (abstract), Kamphius (Kamphius et al; Ophthalmic Research, vol. 35, pages 93-96, 2003) teaches that optineurin gene expression level in the human trabecular meshwork was not changed in response to pressure elevation (see abstract).

Additionally, the post filing date art demonstrates the unpredictability of associating broadly "any" mutation in OPTN, with any type of glaucoma.

While Rezaie teaches that the R545Q mutation appears to be a disease causing mutation in Caucasian patients with adult onset POAG, Alward (Alward et al; Am. J. Ophthalmology, vol. 136, pages 904-910, 2003) teaches that it is likely to be a non disease causing polymorphism with marked ethnic differences in prevalence (see para bridging cols 1 and 2, page 109). Further, while Rezaie teaches that the M98K mutation appeared to be a risk associated alteration for NTG (table 1), Alward teaches that the M98K mutation was associated with a fraction of NTG only in patients with Japanese ethnicity but not in Caucasians (see abstract, col. 2, page 909). Further, Willoughby (Willoughby et al; IOVS, 2004; vol. 45, pages 3122-3130) teaches that the OPTN M98K change, which had been reported as a susceptibility allele for POAG, was studied and "may confer a susceptibility risk to POAG, but does not appear to predispose to JOAG" (see page 3128, col. 1, 2nd full para). Leung (Leung et al; IOVS, September 2003, vol 44, pages 3880-3884), on the other hand, teaches that M98K and R545Q appear to be common polymorphisms in the normal Chinese population (page 3882, col 2). Alternatively, Tang (Tang et al; Human Genetics, vol. 113, pages 276-279; 2003) teaches that none of previously reported NTG risk mutations showed any significant differences among Japanese (see page 278, col. 1, "Discussion"). Further, Tang teaches that 10 out of 392 normal chromosomes contained the G to A mutation at position 1944 in the Japanese population, which differed from the 0 out of 100 chromosomes reported by Rezaie for Caucasians. Wiggs (Wiggs et al; Arch. Ophthalmology. Vol. 121, 2003, pages 1181-1183) teaches analysis of mutations in exons 4 and 5, reported to be

recurrent mutations in patients with NTG, in patients with adult onset POAG, and teaches that these mutations do not appear to be associated with adult onset POAG (see abstract).

The detection of new polymorphisms is an entirely unpredictable art which is empirical in nature, and once these polymorphisms are detected, their association with a phenotype, in this case, different types of glaucoma, must be established before they can be predictably associated with disease, as is broadly claimed. Even if an association is demonstrated between a single nucleotide alteration within a gene and a phenotype, it is not necessarily a predictor that a different polymorphism within the gene will also have the same predictive ability, as exemplified by the teachings in art cited above.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predictive relationship exists between the disclosed alterations and any type of glaucoma in any patient population. Given the unpredictability exemplified in the art, such experimentation would be replete with unpredictable trial and error analysis as the specification does not teach whether a large number of the disclosed mutations are associated with glaucoma. Additionally, for the mutations which show only a single occurrence (table 1) it is not clear if the presence of such mutations was due to chance or would only be observed in such frequencies in a specific population, ie: Caucasian vs Chinese. In a technology that is known to be highly unpredictable,

made more so by the lack of any structure function correlation between the disclosed polymorphisms and glaucoma, the identification of new disease associated alterations is highly unpredictable. Further, the scope of many of the claims requires knowledge of an association between all mutations in the OPTN gene and any type of glaucoma in any human population, which as exemplified by the teachings in the art, is highly unpredictable. The skilled artisan would be required to mutate every position in the OPTN gene, to determine which mutations were and were not associated with glaucoma. As the specification does not teach the function of OPTN, nor how alterations affect the function to provide for an association with glaucoma, the skilled artisan would first have to establish a reliable test for OPTN function, to be able to measure altered function. Although the specification discusses putative domains in the coding sequence with regard to the mutations in table 1 of the specification (para 0148), it is not known, either in the specification or the art, whether such domains are involved in OPTN function, nor how alterations in such regions would affect OPTN function. Conflicting evidence in the art regarding the disease association of the R545Q and M98K alterations in table 1, as well as other alterations in tables 2 and 3, highlights the unpredictable experimentation required for enablement of the instantly pending claims. The art teaches that some of the same alterations which the specification teaches are associated with glaucoma, are not in certain populations. The nature of these conflicting associations is not clear. The experimentation required to enable the full scope of the claimed invention requires a large amount of inventive effort, replete with unpredictable trial and error experimentation, made more so due to the lack of guidance in the specification and the unpredictability of the broadly claimed associations as exemplified by the art.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Indefinite

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 3 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims refer to SEQ ID NOS, however they recite nucleotide positions in terms of "codons". This is confusing because in each case, position 1 of the listed SEQ ID NOS does not refer to the first position of "codon 1". Accordingly, claimed recitation of codon "50" is unclear in the context of a specific SEQ ID NO.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-4 are rejected under 35 U.S.C. 102(a) as being anticipated by Rezaie (Rezaie et al; Science, vol. 295, pages 1077-1079, February 2002).

Rezaie teaches a method of assaying using SSCP analysis, for at least one nucleotide alteration SEQ ID NO: 1 (Genbank Accession number AF420371), including a GAG to AAG alteration at codon 50 (see table 1, Figure 1A) which is a glaucoma associated alteration in optineurin. Rezaie inherently teaches an isolated nucleic acid molecule (sequencing and SSCP analysis) comprising a GAG to AAG mutation in SEQ ID NO: 1, as well as a nucleic acid molecule comprising 10-50 nucleotides of SEQ ID NO: 1 (Figure 1A).

12. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Fodor (US PreGrant Publication 2001/0053519).

Fodor teaches an array of every possible 10 mer nucleic acid molecule. The claims encompass a genus of 10 mer nucleic acid molecules (claims 1-4) as well as an array comprising this genus of nucleic acid molecules, which is anticipated by the teachings of Fodor.

13. Claims 1-4 and 8-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796).

Brennan (cols 9-10) teaches an array of every possible 10 mer nucleic acid molecule. The claims encompass a genus of 10 mer nucleic acid molecules (claims 1-4) as well as an array

comprising this genus of nucleic acid molecules (claims 8-10), which is anticipated by the teachings of Brennan.

14. Claims 1-2, 4, and 8-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Sornasse (Sornasse et al; WO 2001/32927).

Sornasse teaches an isolated nucleic acid molecule (SEQ ID NO: 231) which contains an alteration in at least one nucleotide sequence of SEQ ID NO: 1. One of the alterations, an insertion of a G between nucleotides 405 and 406 of SEQ ID NO: 1, occurs in the open reading of OPTN and would cause a frameshift, changing most of the amino acid sequence of OPTN. This is considered to inherently be indicative of the presence of OPTN associated glaucoma as it changes almost the entire OPTN amino acid sequence. Sornasse teaches microarrays comprising the nucleic acids disclosed, affixed to a solid support (see page 6).

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 8-10 are rejected as being unpatentable over Rezaie in view of Fodor or Brennan.

Rezaie teaches a method of assaying using SSCP analysis, for at least one nucleotide alteration SEQ ID NO: 1 (Genbank Accession number AF420371), including a GAG to AAG alteration at codon 50 (see table 1, Figure 1A) which is a glaucoma associated alteration in optineurin. Rezaie inherently teaches an isolated nucleic acid molecule (sequencing and SSCP analysis) comprising a GAG to AAG mutation in SEQ ID NO: 1, as well as a nucleic acid molecule comprising 10-50 nucleotides of SEQ ID NO: 1 (Figure 1A). Rezaie does not teach an array of nucleic acids attaches to a solid support comprising a nucleic acid molecule comprising 10-50 nucleotides of SEQ ID NO: 1, however Fodor teaches methods of detecting nucleic acid targets using nucleic acid probes attached to a solid support of probes (abstract). Further, Brennan teaches methods of detecting nucleic acid targets using nucleic acid probes attached to a solid support of probes (col. 3). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct probes of 10-50 nucleotides long which include an AAG at codon 50 of SEQ ID NO: 1 to detect mutations in OPTN as taught by Rezaie. The ordinary artisan would have been motivated to construct probes for detection of OPTN mutations taught by Reziae because each of Fodor and Brennan teach that arrays of probes can be used in a number of nucleic acid based applications including target detection and identification.

Conclusion

18. No claims are allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634
7/31/06